

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 5 :</b> <b>A61K 37/02, 37/54, A01N 37/18</b> <b>C12N 11/02, 15/16</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 93/03751</b> <b>(43) International Publication Date:</b> 4 March 1993 (04.03.93)
<b>(21) International Application Number:</b> PCT/US92/06944 <b>(22) International Filing Date:</b> 18 August 1992 (18.08.92)  <b>(30) Priority data:</b> 750,843                      26 August 1991 (26.08.91)                      US  <b>(71) Applicant:</b> ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).  <b>(72) Inventors:</b> FU LU, Mou-Ying ; 195 Grafton Court, Lake Bluff, IL 60044 (US). REILAND, Thomas, L. ; 33974 North Lake Shore Drive, Gages Lake, IL 60030 (US).  <b>(74) Agents:</b> GORMAN, Edward, H., Jr. et al.; Abbott Laborat- ories, CHAD 0377/AP6D-2, One Abbott Park Road, Ab- bott Park, IL 60064-3500 (US).		<b>(81) Designated States:</b> AU, CA, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> COMPOSITIONS AND METHODS FOR THE SUBLINGUAL OR BUCCAL ADMINISTRATION OF THER- APEUTIC AGENTS  <b>(57) Abstract</b>  Pharmaceutical compositions for the sublingual or buccal administration of therapeutic agents (particularly polypeptides) which are normally degraded upon oral administration comprise such a therapeutic agent, a solvent, optionally a cosolvent and/or hydrogel, and an oral mucosal membrane transport enhancing agent which is selected from the group consisting of essential and volatile oils and inorganic and organic acids.		

Best Available Copy

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	MN	Mongolia
AU	Australia	FR	France	MR	Mauritania
BB	Barbados	GA	Gabon	MW	Malawi
BE	Belgium	GB	United Kingdom	NL	Netherlands
BF	Burkina Faso	GN	Guinea	NO	Norway
BG	Bulgaria	GR	Greece	NZ	New Zealand
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	PT	Portugal
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	RU	Russian Federation
CG	Congo	KP	Democratic People's Republic of Korea	SD	Sudan
CH	Switzerland	KR	Republic of Korea	SE	Sweden
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovak Republic
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CS	Czechoslovakia	LU	Luxembourg	SU	Soviet Union
CZ	Czech Republic	MC	Monaco	TD	Chad
DE	Germany	MG	Madagascar	TG	Togo
DK	Denmark	ML	Mali	UA	Ukraine
ES	Spain			US	United States of America

## COMPOSITIONS AND METHODS FOR THE SUBLINGUAL OR BUCCAL ADMINISTRATION OF THERAPEUTIC AGENTS

5

### Technical Field of the Invention

The present invention relates to pharmaceutical compositions and a method of using such compositions. More particularly, the present invention concerns pharmaceutical compositions useful for the sublingual or buccal administration of therapeutic agents which are otherwise degraded by enzymatic or protolytic action when administered orally, and to a method of using such compositions.

10

### Background of the Invention

Orally administered therapeutic agents are rapidly transported to the stomach and small intestine for absorption across gastro-intestinal mucosal membranes into the blood. The efficiency of absorption of a therapeutic agent (i.e. the ratio of the amount entering the blood to the amount administered) following oral administration of many drugs can be low because of several factors which serve to metabolize the administered chemical. Low absorption efficiency is particularly problematic with polypeptide therapeutic agents.

15

The gastrointestinal tract secretes a variety of agents that metabolize polypeptides. Exemplary of such catabolic agents are pepsin, trypsin, chymotrypsin, carboxypolypeptidases, aminopolypeptidases and dipeptidases. Polypeptides that escape catabolism in the stomach and small intestine are transported across the cells lining the gastrointestinal tract into the portal circulation, which carries absorbed polypeptides to the liver. Absorbed polypeptides are subject to further degradation by a myriad of hepatic metabolic events. Such hepatic degradation of absorbed materials from the blood before such materials enter the general systemic circulation is known in the pharmaceutical art as the "first pass effect".

20

25

As a result of these factors causing low absorptive efficiency of orally administered therapeutic agents, particularly polypeptides, if the choice of the route of administration is the oral route, it is necessary to administer large dosages of such polypeptides. This is costly in many cases and inefficient. Alternatively, such therapeutic agents can be administered via other routes such as intravenously, subcutaneously or intraperitoneally. These alternate routes are all invasive by nature and can involve pain and discomfort to a subject. There is, therefore, a pressing

30

35

need for new, efficient, cost-effective and noninvasive methods and compositions for the administration to patients of therapeutic agents which would be otherwise degraded if administered orally.

The present invention provides novel compositions and methods for the  
5 sublingual administration of therapeutic agents.

#### Brief Description of the Drawings

In the drawings, which form a part of this disclosure:

FIGURE 1 is a plot of plasma leuprolide concentration vs. time following the  
10 sublingual administration of seven (A-G) different liquid compositions containing 50 mg/ml of the luteinizing hormone releasing hormone (LHRH) agent leuprolide acetate. Anesthetized dogs were administered 0.1 ml/10 kg body wt of compositions A-G of Table 1 and the plasma levels of leuprolide determined by RIA at the indicated times.

15 FIGURE 2 is a plot of plasma leuprolide concentration vs. time following the sublingual administration of liquid compositions comprising 2.5 percent by weight Klucel LF<sup>TM</sup>, an aqueous-alcohol solvent having 0 percent (EtOH:H<sub>2</sub>O 0:100), 50 percent (EtOH:H<sub>2</sub>O 50:50) 65 percent (EtOH:H<sub>2</sub>O 65:35) or 80 (EtOH:H<sub>2</sub>O 80:20)  
20 by volume ethanol (EtOH). The dose of administered leuprolide acetate and the measurement of plasma leuprolide concentration are the same as described for FIGURE 1.

FIGURE 3 is a plot of plasma leuprolide concentration vs. time following the  
25 sublingual administration of a liquid composition comprising 50 mg/ml leuprolide acetate, 2.5 percent by weight hydroxypropylmethyl cellulose (HPMC), an aqueous-alcohol solvent having 80 percent by volume ethanol and 0, 5 or 10 percent by weight benzoic acid. The dose of administered leuprolide acetate and the measurement of plasma leuprolide concentration are the same as described for  
30 FIGURE 1.

FIGURE 4 is a bar graph of area under the curve (AUC 0-8 hours) vs. peppermint oil concentration (percent by volume). Dogs were sublingually administered 0.1 ml/10 kg body weight of a liquid composition comprising 50 mg/ml leuprolide  
35 acetate, an aqueous alcohol solvent having 80 percent by volume ethanol and 0, 0.5, 2.0, 2.5, 5 or 10 percent by volume peppermint oil.

### Brief Summary of the Invention

In its principal aspect, the present invention provides liquid compositions for the sublingual or buccal administration of therapeutic agents which are normally degraded upon oral administration, especially polypeptides, comprising said therapeutic agent and a carrier which comprises a solvent system and an oral mucosal membrane transport enhancing agent. The solvent system comprises a non-toxic alcohol which is from about 50 percent to about 95 percent w/v of the total volume of the carrier. The balance of the carrier comprises from about 0.5 percent w/v to about 20 percent w/v, based upon the total volume of the carrier, of a mucosal membrane transport enhancing agent and, optionally, a cosolvent and/or a hydrogel. The cosolvent, when present, comprises from about 5 percent w/v to about 50 percent w/v of the carrier, and the optional hydrogel, when present, comprises from about 1 percent w/v to about 5 percent w/v of the carrier. The oral mucosal membrane transport enhancing agent is selected from the group consisting of essential and volatile oils and pharmaceutically acceptable, non-toxic inorganic or organic acids, and comprises between about 0.5 percent w/v and 50 percent w/v of the carrier.

In another aspect, the present invention provides a method for the sublingual or buccal administration of a therapeutic agent, particularly a polypeptide, to a patient comprising preparing a liquid composition of this invention and administering said liquid composition under the tongue of the patient.

### Detailed Description Of The Invention

The liquid compositions of the present invention are particularly suited for the sublingual or buccal administration of sensitive therapeutic agents, particularly polypeptide therapeutic agents, which are normally degraded upon oral administration. As used herein, the term "polypeptide" means a compound comprising a sequence of amino acid residues connected by peptide linkages. Polypeptides can have from 2 to about 150 amino acid residues. Thus, for the purpose of the present invention, polypeptide is inclusive of what is generally referred to in the art as peptide, polypeptide and protein. The amino acid residue sequence can be connected to lipids or carbohydrates in the form of lipoproteins or glycoproteins. Preferably, polypeptides used in the present invention are drugs, medicaments and other agents having a pharmacological or physiological action in an animal subject. Representative polypeptides which can be sublingually or

buccally administered employing the formulations of the present invention include growth hormone, insulin, luteinizing hormone releasing hormone (5-oxo-Pro-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH<sub>2</sub>, LHRH -Sequence ID No. 1), oligopeptide therapeutic agents of from seven to ten amino acid residues which control the release of LHRH such as and 5-oxo-Pro-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-N-ethylamide (leuprolide - Sequence ID No. 2), cholecystokinin (Lys-Ala-Pro-Ser-Gly-Arg-Met-Ser-Ile-Val-Lys-Asn-Leu-Gln-Asn-Leu-Asp-Pro-Ser-Arg-Ile-Ser-Asp-Arg-Asp-Tyr(S03H)-Met-Gly-Trp-Met-Asp-Phe-NH<sub>2</sub>, CCK - Sequence ID No. 3)) and and therapeutic agents which control the release of CCK such as BOC-Trp-ε-(2-methylphenylaminocarbonyl)Lys-Asp-(N-methyl)Phe-NH<sub>2</sub> (Sequence ID No. 4).

The compositions of this invention comprise the therapeutic agent dissolved or dispersed in a carrier which comprises a solvent, an optional cosolvent, an optional hydrogel, and an oral mucosal membrane transport enhancing agent. The solvent comprises from about 50 percent w/v to about 95 percent w/v, preferably from about 55 percent w/v to about 80 percent w/v of the carrier of a non-toxic alcohol. Non-toxic alcohols useful in the formulations of the present invention are selected from those well known in the art and include ethanol, isopropanol, stearyl alcohol, propylene glycol, polyethylene glycol (preferably having a molecular weight of up to about 650 daltons), and the like. Non-toxic alcohols for use in pharmaceutical formulations are well known in the art (cf., for example, Handbook of Pharmaceutical Excipients, pub. by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (1986)). Preferably, the non-toxic alcohol is ethanol. Most preferably, the non-toxic alcohol is ethanol and is present at a concentration of about 80 percent w/v of the carrier.

The cosolvent is selected from water or a pharmaceutically acceptable oil. Suitable oils for use in the compositions of this invention include mineral oil, Neobee™ oil, olive oil, sunflower oil, corn oil, peanut oil and the like.

Hydrogels suitable for use in the compositions of this invention include hydroxypropyl cellulose, hydroxypropyl methyl cellulose, sodium carboxymethylcellulose (CMC), polyacrylic acid, poly(methyl methacrylic acid), and the like. When present in the compositions of this invention, the hydrogel comprises from about 0.1 to about 50 percent w/v of the carrier.

The oral mucosal membrane transport enhancing agent is included in the compositions of the present invention to facilitate the absorption of the therapeutic agent across the mucosal tissues in the oral cavity and directly into the blood stream

of the subject. Tissue transport enhancing agents suitable for use in the present compositions are selected from essential or volatile oils or from non-toxic, pharmaceutically acceptable inorganic and organic acids.

Essential or volatile oils which may be employed in the compositions are selected from peppermint oil, spearmint oil, menthol, pepper oil, eucalyptus oil, cinnamon oil, ginger oil, fennel oil, dill oil and the like. The essential or volatile oil, when employed as the oral mucosal membrane transport enhancing agent in the compositions of the present invention is present in a concentration ranging between about 0.5 percent w/v and 50 percent w/v of the carrier. The preferred essential oil is peppermint oil, present in a concentration of between about 1 percent w/v and 5 percent w/v of the carrier.

Suitable inorganic and organic acids are selected from hydrochloric acid, phosphoric acid, aromatic and aliphatic monocarboxylic or dicarboxylic acids of from two to thirty carbon atoms such as acetic acid, citric acid, lactic acid, oleic acid, linoleic acid, lauric acid, palmitic acid, benzoic acid, salicylic acid, and the like. By the term "aromatic" carboxylic acid is meant any acid which contains the 6-membered carbocyclic ring system characteristic of benzene, and by the term "aliphatic" carboxylic acid is meant any acid which contains a straight-chain or branched chain saturated or unsaturated hydrocarbon backbone. The preferred organic acid in compositions of this invention is benzoic acid. Liquid compositions containing benzoic acid are known to enhance the bioavailability of polypeptides in such compositions when administered sublingually (See Example 3).

When the compositions of the present invention contain an acid as the oral mucosal membrane enhancing agent, the pH of the composition preferably ranges between about pH 3.0 and about pH 7.0. The pH of the compositions may be adjusted or maintained by the use of pharmaceutically acceptable, non-toxic buffer systems generally known in the art. The selection of a particular acid is dependent inter alia upon the nature of the anionic component of the acid. Thus, the subject being administered the liquid composition of the invention may be in need of phosphate, chloride, lactate and the like. Conversely, the administration of a particular anion may be contraindicated in some subjects. The concentration of acid in the liquid compositions of the present invention is dependent upon the nature of the acid (i.e.,  $pK_a$  and dissociation constant) as well as the desired pH. When the acid is benzoic acid, a preferred concentration is from about 4 to about 10 percent by weight.

The liquid composition can be formulated into a liquid spray, a liquid drop, a gel or a paste. The desired consistency is achieved by including in the liquid composition one or more hydrogels, substances that absorb water and produce gels of varying viscosity. Hydrogels suitable for use in pharmaceutical preparations are well known in the art. See, e.g. Handbook of Pharmaceutical Excipients, pub. by The American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (1986) and Handbook of Water-Soluble Gums and Resins, ed. by R.L. Davidson, McGraw-Hill Book Co., New York, N.Y. (1980).

Suitable hydrogels for use in the compositions of this invention include hydroxypropyl cellulose, hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose, polyacrylic acid, poly(methyl methacrylic acid) (PMMA). Preferred hydrogels are cellulose ethers such as hydroxyalkylcellulose and hydroxyalkylalkylcellulose compounds. A preferred hydroxyalkylcellulose is hydroxypropyl cellulose. Hydroxypropyl cellulose is commercially available in a wide range of viscosity grades sold under the tradename Klucel™ (Hercules, Ltd., London, England). The concentration of the hydroxyalkylcellulose is dependent upon the particular viscosity grade used and the desired viscosity of the liquid composition. For example, where the desired viscosity is less than about 1000 centipoise (cps), hydroxypropyl cellulose having an average molecular weight of about 60,000 daltons (i.e., Klucel EF™) can be used. Where the desired viscosity is from about 1000 to about 2500 cps, higher viscosity grades of hydroxypropyl cellulose can be used (i.e., Klucel L™ and Lucel G™). Preferably, the concentration of hydroxypropyl cellulose is from about 1 to about 5 percent w/v and, more preferably from about 2 to about 3 percent w/v of the carrier.

Hydroxyalkylalkylcellulose ethers are a class of water-soluble hydrogels derived from etherification of cellulose. As used herein in reference to this class of hydrogels, the term "alkyl" means C<sub>1</sub>-C<sub>6</sub> alkyl where alkyl refers to linear or branched chains having 1 to 6 carbon atoms, which can be optionally substituted as herein defined. Representative alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl and the like.

Exemplary hydroxyalkylalkylcelluloses are hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose and hydroxybutylmethyl cellulose. Hydroxypropylmethyl cellulose (HPMC) is preferred. HPMC is commercially available (i.e., Aldrich Chem. Co., Ltd. Dorset, England and Dow Chem. Co., Midland, MI, USA) in a wide range of viscosity grades. In addition to increasing viscosity, hydroxyalkylalkylcelluloses can serve as a stabilizing, suspending and emulsifying



agent. The concentration of hydroxyalkylalkylcellulose in a liquid composition of this invention is dependent inter alia on its intended use (i.e., stabilizer, emulsifier, viscosity-increasing agent) and its viscosity grade.

In one preferred embodiment of the present invention, the formulation  
5 comprises between 1 mg/ml and 100 mg/ml of an agent effective to control the release of luteinizing hormone releasing hormone or a pharmaceutically acceptable salt thereof; a carrier comprising between about 55 and about 80 percent w/v ethanol, about 2 to about 5 percent w/v of hydroxypropyl cellulose hydrogel; and an oral mucosal membrane transport enhancing agent comprising about 10 and about  
10 25 percent w/v benzoic acid; all percentages based upon the total volume of carrier.

In another preferred embodiment of the present invention, the formulation comprises between 1 mg/ml and 100 mg/ml of an agent effective to control the release of luteinizing hormone releasing hormone or a pharmaceutically acceptable salt thereof; a carrier comprising between about about 55 and about 80 percent w/v  
15 ethanol, about 2 to about 5 percent w/v of hydroxypropyl cellulose hydrogel; and an oral mucosal membrane transport enhancing agent comprising between about 5 and about 20 percent w/v benzoic acid and between about 1 to about 5 percent w/v peppermint oil; all percentages based upon the total volume of carrier.

In another aspect, the present invention comprises a method of sublingually  
20 administering a therapeutic agent, preferably a polypeptide, to a patient comprising preparing a liquid composition of said therapeutic agent and an aqueous-alcohol solvent having from about 50 to about 80 percent by volume of a non-toxic alcohol and a pH from about 4.0 to about 7.0 and administering an effective amount of said liquid composition to the underside of the tongue of said patient. The liquid  
25 compositions contemplated for use in this method are those set forth above.

The liquid composition is administered to the patient under the tongue. The sublingual mucosae, located on the underside of the tongue, provide expeditious entry of the polypeptide-containing liquid composition into the general bloodstream through the sublingual tributary veins. The therapeutic agent is first absorbed  
30 through the sublingual mucosae into the sublingual veins. From there, the polypeptide is pumped into the right side of the heart and then into the lungs where the blood is oxygenated. From there the oxygenated blood would carry the therapeutic agent back into the left side of the heart and out through the systemic arteries for distribution throughout the body.

35 The liquid composition can be administered under the tongue by placing one or more drops underneath the tongue or by spraying the underside of the tongue

with a preselected volume of the liquid composition. Preferably, the administered volume, either drops or spray, is less than about 1 ml.

The following Examples are provided to enable one skilled in the art to practice the present invention and are merely illustrative of the invention. They  
5 should not be read as limiting the scope of the invention as it is defined by the appended claims.

### Example 1

#### Bioavailability of Leuprolide Acetate Administered Sublingually

10 The liquid compositions of Table 1 were prepared by dissolving the synthetic polypeptide leuprolide acetate in the liquid compositions such that the leuprolide acetate concentration was about 50 mg/ml. Leuprolide acetate has the formula: 5-oxo-L-prolyl-L-histidyl-L-tryptophanyl-L-seryl-L-tyrosyl-D-leueyl-L-leueyl-L-arginyl-L-prolyl-ethylamide monoacetate.

15

TABLE I

A.	Leuprolide acetate Urea Klucel EF <sup>TM</sup>	50 mg/ml 10% (w/v) 2% (w/v)
B.	Leuprolide acetate Benzoic acid Klucel EF <sup>TM</sup> Ethanol	50 mg/ml 5% (w/v) 2% (w/v) 50% (w/v)
C.	Leuprolide acetate Klucel EF <sup>TM</sup>	
D.	Leuprolide acetate Hydroxylpropyl cyclodextrin	
E.	Leuprolide acetate Ethanol Klucel EF <sup>TM</sup>	
F.	Leuprolide acetate Peppermint oil Ethanol Klucel EF <sup>TM</sup>	
G.	Leuprolide acetate Urea L-Arginine HCl Klucel EF <sup>TM</sup>	

5 The liquid compositions were sublingually administered to dogs by placing 0.1 ml/10 Kg. body weight between the underside of the tongue and the bottom of the oral cavity. In this way, each dog received a dose of leuprolide acetate equal to 0.5 mg/kg. body weight. The plasma level of leuprolide was determined before and 0.25, 0.5, 1, 2, 4, and 6 hours after sublingual administration of the liquid compositions. The results of these studies are summarized in Figure 1 and Table 2.

10

TABLE 2

Composition From Table 1	AUC (0-6 hours)	% Bioavailability*
A	34	2.1
B	318	19.4
C	51	3.1
D	17	1.1
E	353	21.5
F	1385	84.5
G	21	1.3

\*Bioavailability is calculated based on iv data

5

In this and subsequent Examples, bioavailability is calculated and expressed either in terms of Area Under Curve (AUC) or as percent (%) bioavailability. AUC is determined by calculating the area under the curve of plots of time (X-axis) versus plasma concentration (Y-axis) of the administered polypeptide. Typically, AUC is determined over a 6 (0-6) or 8 (0-8) hour period. Percent bioavailability is calculated as the ratio

10

$$\frac{\text{AUC for sublingual administration}}{\text{AUC for the same dose administered sc or iv}} \times 100$$

Increases in AUC and/or bioavailability indicate increased bioavailability of the administered polypeptide.

15

The data in Figure 1 and Table 2 show that ethanol in concentrations from 50 (compositions B, Table 1) to 80 percent by volume (compositions E and F, Table 1) increased the bioavailability of sublingually administered leuprolide.

20

### Example 2

#### Effects of Ethanol on Bioavailability of Sublingually Administered Leuprolide Acetate

25

These studies were designed to test the effects of ethanol concentration on the bioavailability of sublingually administered leuprolide acetate. Liquid compositions comprising 2 percent by weight peppermint oil, 2.5 percent by weight

## 1 1

Klucel LF<sup>TM</sup>, 50 mg/ml leuprolide acetate and an aqueous-alcohol solvent having 0, 50, 65 or 80 percent by volume ethanol were prepared.

Aliquots of these liquid compositions (0.1 ml/10 Kg. body weight) were sublingually administered to anesthetized dogs using a drop or spray dispenser.

5 Plasma levels of leuprolide were measured by RIA in venous blood samples before and 0.33, 0.67, 1, 2, 3, 4, 6 and 8 hours after administration. The results of these studies are shown in Figure 2 and Table 3.

TABLE 3

10

Ethanol (%) (w/v)	Bioavailability (%)*
80	8.7
65	5.0
50	2.0
0	2.0

\*Bioavailability was calculated based on the sc absorption.

15 The data in Figure 2 and Table 3 show that ethanol concentration causes a dose dependent increase in the bioavailability of sublingually administered leuprolide.

## Example 3

Effects of pH on Bioavailability Of Sublingually Administered Leuprolide Acetate

20 Liquid compositions were prepared to comprise 50 mg/ml leuprolide acetate, 2.5 percent by weight HPMC, an aqueous-alcohol solvent having 80 percent by volume ethanol and 0, 5 or 10 percent by weight benzoic acid. The pH's of liquid compositions having 0, 5 or 11) percent by weight benzoic acid were about 6.8, 5.6 and 4.4 respectively. The results of these studies are shown in Figure 3. The data in  
25 Figure 3 show that the bioavailability of leuprolide is directly proportional to benzoic acid concentration. Additional studies were performed to show that the effects of benzoic acid on bioavailability were due to changes in pH rather than an inherent property of benzoic acid *per se*. Liquid compositions comprising 50 mg/ml leuprolide acetate, 2 percent by weight peppermint oil, an aqueous-alcohol solvent  
30 having 65 percent by volume ethanol and 4 percent by weight benzoic acid were

1 2

prepared. In one such composition the pH value was adjusted to a value of about 7.0 with NaOH. In another such composition, the pH value was not adjusted and was about 5.6.

5 The liquid compositions were sublingually administered to dogs (0.1 mg/10 kg body wt) and the plasma levels of leuprolide measured over 8 hours. The results of this study are summarized in Table 4.

TABLE 4

Ethanol (% w/v)	Peppermint Oil (% w/v)	Benzoic Acid (% w/v)	pH	Percent Bioavailability
65/35			6.2	5.0
65/35	2		6.2	16.9
65/35	2	4	5.6	24.5
65/35	2	4	7.0 (Adjusted)	2.7

10 \* Bioavailability was calculated based on the sc absorption.

The data in Table 4 show that the enhanced bioavailability associated with benzoic acid is a function of pH.

15

#### Example 4

##### Effects Of Peppermint Oil On The Bioavailability Of Sublingually Administered Leuprolide Acetate

20 Liquid compositions comprising 50 mg/ml leuprolide acetate, an aqueous-alcohol solvent having 80 percent by volume ethanol and 0, 0.5, 2, 2.5, 5 and 10 percent by volume peppermint oil were prepared and sublingually administered to dogs at a dose of 0.1 ml/10 kg body weight. Plasma leuprolide levels were monitored for 8 hours following administration. The results of this study are shown  
25 in Figure 4.

The data in Figure 4 show that peppermint oil at a concentration of about 2 to 10 percent by volume increases the bioavailability of sublingually administered leuprolide acetate.

**Example 5****Bioavailability Of Sublingually Administered Deslorelin™**

The synthetic polypeptide Deslorelin™ (Sigma Chem Co., St. Louis, MO), pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-NHET (Sequence ID No. 4), was dissolved in either saline or a liquid composition comprising 2 percent by volume peppermint oil, 2.5 percent by weight Klucel LF™, 4 percent by weight benzoic acid and an aqueous-alcohol solvent having 65 percent by volume ethanol such that the concentration of Deslorelin™ was about 68 mg/ml. About 0.1 ml of the Deslorelin™ compositions were sublingually administered to anesthetized dogs and the plasma level of Deslorelin™ measured by RIA immediately before and 0.33, 0.67, 1, 2, 3, 4, 6 and 8 hours after administration.

Where dogs received Deslorelin™ in saline, the maximum plasma level observed was about 1.5 ng/ml and the AUC (0-8 hours) was about 2 hr-ng/ml. In marked contrast, dogs receiving Deslorelin™ in a liquid composition of the present invention had a maximum plasma Deslorelin™ level of about 290 ng/ml and an AUC (0-8 hours) of about 800 hr-ng/ml. These data show that a liquid composition of this invention markedly increases the bioavailability of sublingually administered Deslorelin™.

14

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- (i) APPLICANT: Fu Lu, Mou-Ying  
Reiland, Thomas L.
- 5 (ii) TITLE OF INVENTION: "Compositions and Methods  
for the Sublingual or Buccal  
Administration of Therapeutic Agents"
- (iii) NUMBER OF SEQUENCES: 4
- (iv) CORRESPONDENCE ADDRESS:
- 10 (A) ADDRESSEE: Edward H. Gorman, Jr., Dept.  
377-AP6D
- (B) STREET: One Abbott Park Road
- (C) CITY: Abbott Park
- (D) STATE: Illinois
- 15 (E) COUNTRY: United States of America
- (F) ZIP: 60064-3500
- (v) COMPUTER READABLE FORM:
- (A) MEDIUM TYPE: Floppy disk
- (B) COMPUTER: IBM PC compatible
- 20 (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: PatentIn Release #1.0, Version  
#1.25
- (vi) CURRENT APPLICATION DATA:
- (A) APPLICATION NUMBER:
- 25 (B) FILING DATE:
- (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
- (A) NAME: Janssen, Jerry F.
- (B) REGISTRATION NUMBER: 29,175
- 30 (C) REFERENCE/DOCKET NUMBER: 4848.US.01
- (ix) TELECOMMUNICATION INFORMATION:
- (A) TELEPHONE: (708) 938-7742
- (B) TELEFAX: (708) 937-9556

35



15

## (2) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids

(B) TYPE: amino acid

5 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (ix) FEATURE:

(A) NAME/KEY: Modified-site

10 (B) LOCATION: 1

(D) OTHER INFORMATION: /note= "Xaa at position  
1 is 5-oxo-proline"

## (ix) FEATURE:

(A) NAME/KEY: Modified-site

15 (B) LOCATION: 10

(D) OTHER INFORMATION: /note= "Xaa at position  
10 is glycine"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Xaa His Trp Ser Tyr Gly Leu Arg Pro Xaa

20 1 5 10

## (2) INFORMATION FOR SEQ ID NO:2:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

25 (B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (ix) FEATURE:

30 (A) NAME/KEY: Modified-site

(B) LOCATION: 1

(D) OTHER INFORMATION: /note= "Xaa at position  
1 is 5-oxo-proline"

35

16

## (ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 6

(D) OTHER INFORMATION: /note= "Xaa at position  
6 is D-leucine"

5

## (ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 9

(D) OTHER INFORMATION: /note= "Xaa at position  
9 is proline-N-ethylamide"

10

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Xaa His Trp Ser Tyr Xaa Leu Arg Xaa

1

5

15

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 amino acids

(B) TYPE: amino acid

20

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (ix) FEATURE:

(A) NAME/KEY: Modified-site

25

(B) LOCATION: 26

(D) OTHER INFORMATION: /note= "xaa at position  
26 is tyrosine-4-sulfonate"

## (ix) FEATURE:

(A) NAME/KEY: Modified-site

30

(B) LOCATION: 32

(D) OTHER INFORMATION: /note= "Xaa at position  
32 is phenylalaninamide"

35

17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Lys Ala Pro Ser Gly Arg Met Ser Ile Val Leu Asn Leu Gln

1                      5                      10

Asn Leu Asp Pro Ser Arg Ile Ser Asp Arg Asp Xaa Met Gly

**5      15                          20                          25**

Trp Met Asp Xaa

30

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

15 (ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 1

(D) OTHER INFORMATION: /note= "Xaa at position 1 is pyroglutamic acid"

20 (ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 6

(D) OTHER INFORMATION: /note= "Xaa at position 6 is D-tryptophan"

25 (ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 9

(D) OTHER INFORMATION: /note= "Xaa at position  
9 is proline N-ethylamide"

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Xaa His Trp Ser Tyr Xaa Leu Arg Xaa

1 5

18

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

5 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (ix) FEATURE:

(A) NAME/KEY: Modified-site

10 (B) LOCATION: 1

(D) OTHER INFORMATION: /note= "Xaa at position  
1 is pyroglutamic acid"

## (ix) FEATURE:

(A) NAME/KEY: Modified-site

15 (B) LOCATION: 6

(D) OTHER INFORMATION: /note= "Xaa at position  
6 is D-tryptophan"

## (ix) FEATURE:

(A) NAME/KEY: Modified-site

20 (B) LOCATION: 9

(D) OTHER INFORMATION: /note= "Xaa at position  
9 is proline N-ethylamide"

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Xaa His Trp Ser Tyr Xaa Leu Arg Xaa

25

1

5

## WE CLAIM:

1. A pharmaceutical composition for the sublingual or buccal administration of therapeutic agents which are degraded upon oral administration comprising
  - a) said therapeutic agent,
  - b) a pharmaceutically acceptable carrier comprising a solvent system comprising from about 50 percent w/v to about 95 percent w/v of a non-toxic alcohol and from about 0.5 percent w/v to about 50 percent w/v of an oral mucosal membrane transport enhancing agent;  
said percentages based upon the total volume of carrier.
2. A pharmaceutical composition as defined by Claim 1 wherein said therapeutic agent is selected from LHRH and polypeptides effective to control the release of luteinizing hormone releasing hormone (LHRH).
3. A pharmaceutical composition as defined by Claim 1 wherein the carrier further comprises from about 5 percent w/v to about 50 percent w/v of a cosolvent selected from the group consisting of water or a pharmaceutically acceptable mineral or vegetable oil, based upon the volume of carrier.
4. A pharmaceutical composition as defined by Claim 1 further comprising between about 0.1 and about 50 percent w/v of a hydrogel.
5. A pharmaceutical composition as defined by Claim 1 wherein the non-toxic alcohol is present in an amount ranging between about 55 percent w/v and about 80 percent w/v of the carrier.
6. A pharmaceutical composition as defined by Claim 1 wherein the non-toxic alcohol is selected from ethanol, propylene glycol, and poly(ethylene glycol) having a molecular weight of up to about 650 daltons.
7. A pharmaceutical composition as defined by Claim 1 wherein said oral mucosal membrane transport enhancing agent comprises from about 2 percent w/v to about 20 percent w/v of said carrier.

20

8. A pharmaceutical composition as defined by Claim 1 wherein said mucosal membrane transport enhancing agent is selected from the group consisting of peppermint oil, spearmint oil, menthol, pepper oil, eucalyptus oil, cinnamon oil, ginger oil, fennel oil, and dill oil, hydrochloric acid, phosphoric acid, acetic acid, citric acid, lactic acid, oleic acid, linoleic acid, lauric acid, palmitic acid, benzoic acid, and salicylic acid.
9. A pharmaceutical composition as defined by Claim 1 comprising
- a) between 1 mg/ml and 100 mg/ml of a therapeutic agent selected from the group consisting of 5-oxoPro-His-Trp-Ser-Tyr-Gly-Leu-Arg Pro-Gly-NH<sub>2</sub> (LHRH -Sequence ID No. 1) and 5-oxoPro-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-N-ethylamide (Sequence ID No. 2) or a pharmaceutically acceptable salt thereof;
  - b) a carrier comprising
    - 1) between about 55 and about 80 percent w/v ethanol,
    - 2) about 2 to about 5 percent w/v of hydroxypropyl cellulose hydrogel; and
  - c) an oral mucosal membrane transport enhancing agent comprising about 10 and about 25 percent w/v benzoic acid; all percentages based upon the total volume of carrier.
10. A pharmaceutical composition as defined by Claim 1 comprising
- a) between 1 mg/ml and 100 mg/ml of a therapeutic agent selected from the group consisting of S-oxoPro-His-Trp-Ser-Tyr-Gly-Leu-Arg Pro-Gly-NH<sub>2</sub> (LHRH -Sequence ID No. 1) and S-oxoPro-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-N-ethylamide (Sequence ID No. 2) or a pharmaceutically acceptable salt thereof;
  - b) a carrier comprising
    - 1) between about 55 and about 80 percent w/v ethanol,
    - 2) about 2 to about 5 percent w/v of hydroxypropyl cellulose hydrogel; and

21

- 15                   c)     an oral mucosal membrane transport enhancing agent  
                          comprising between about 5 and about 20 percent w/v  
                          benzoic acid and between about 1 to about 5 percent w/v  
                          peppermint oil;  
                  all percentages based upon the total volume of carrier.

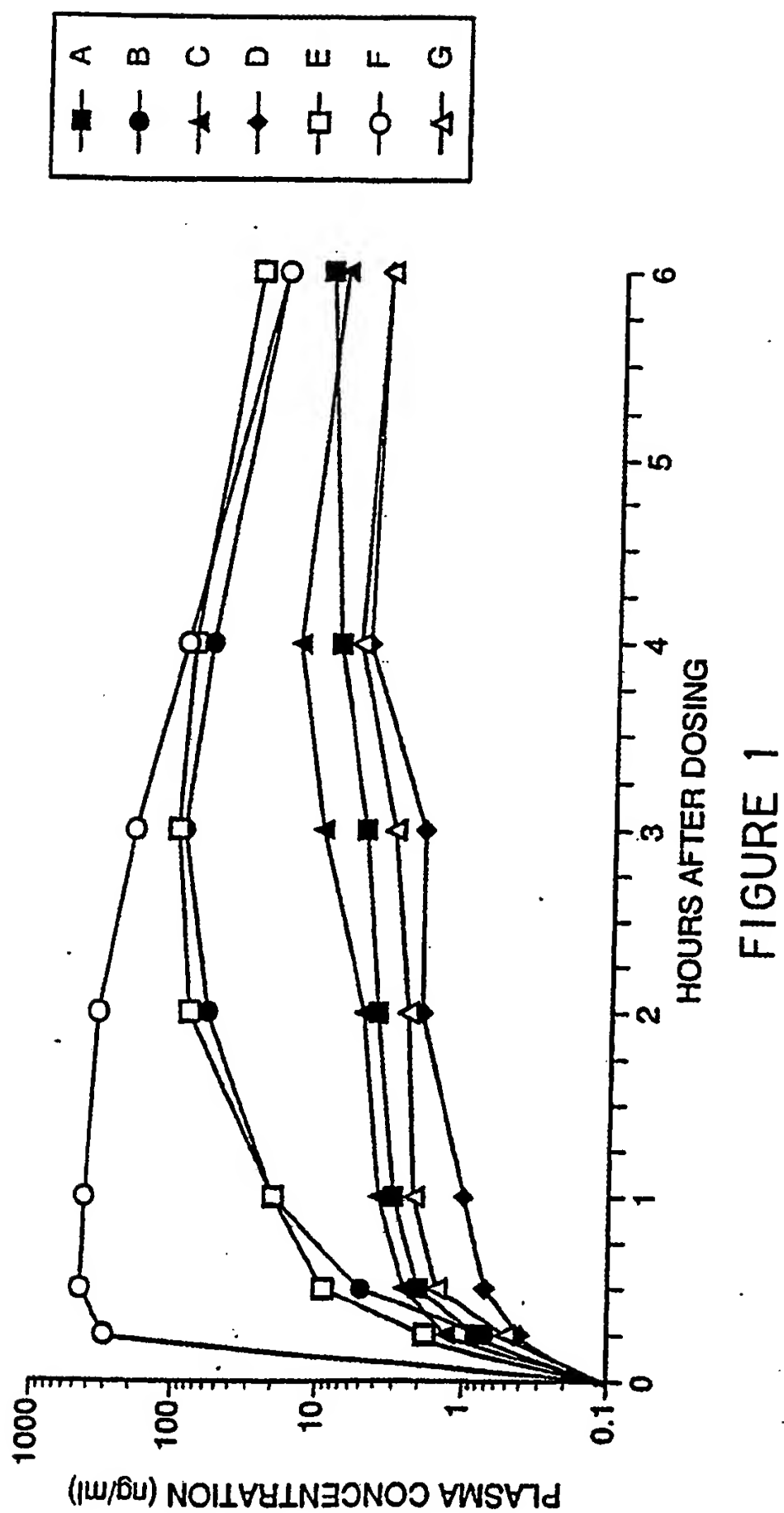


FIGURE 1



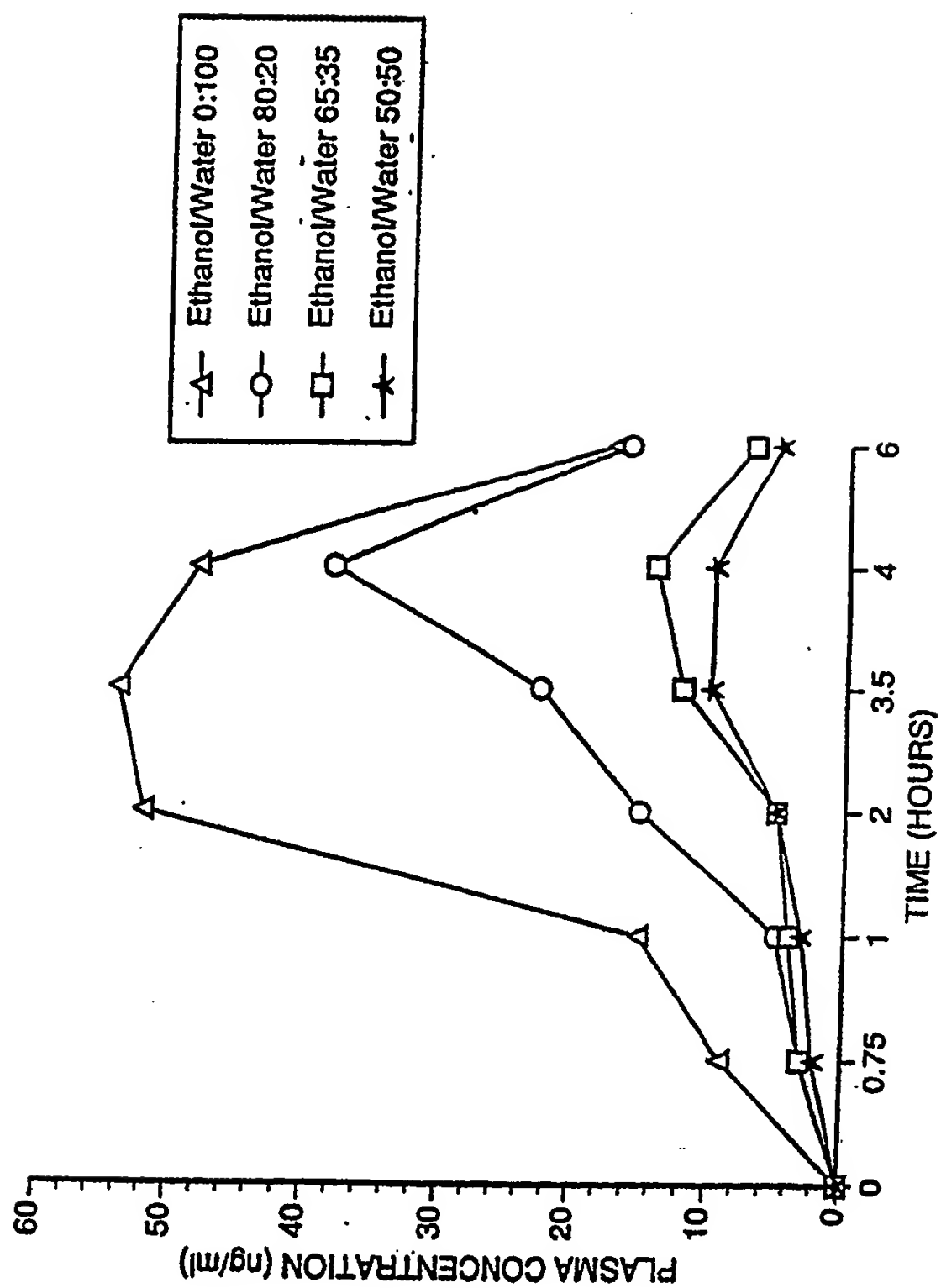


FIGURE 2

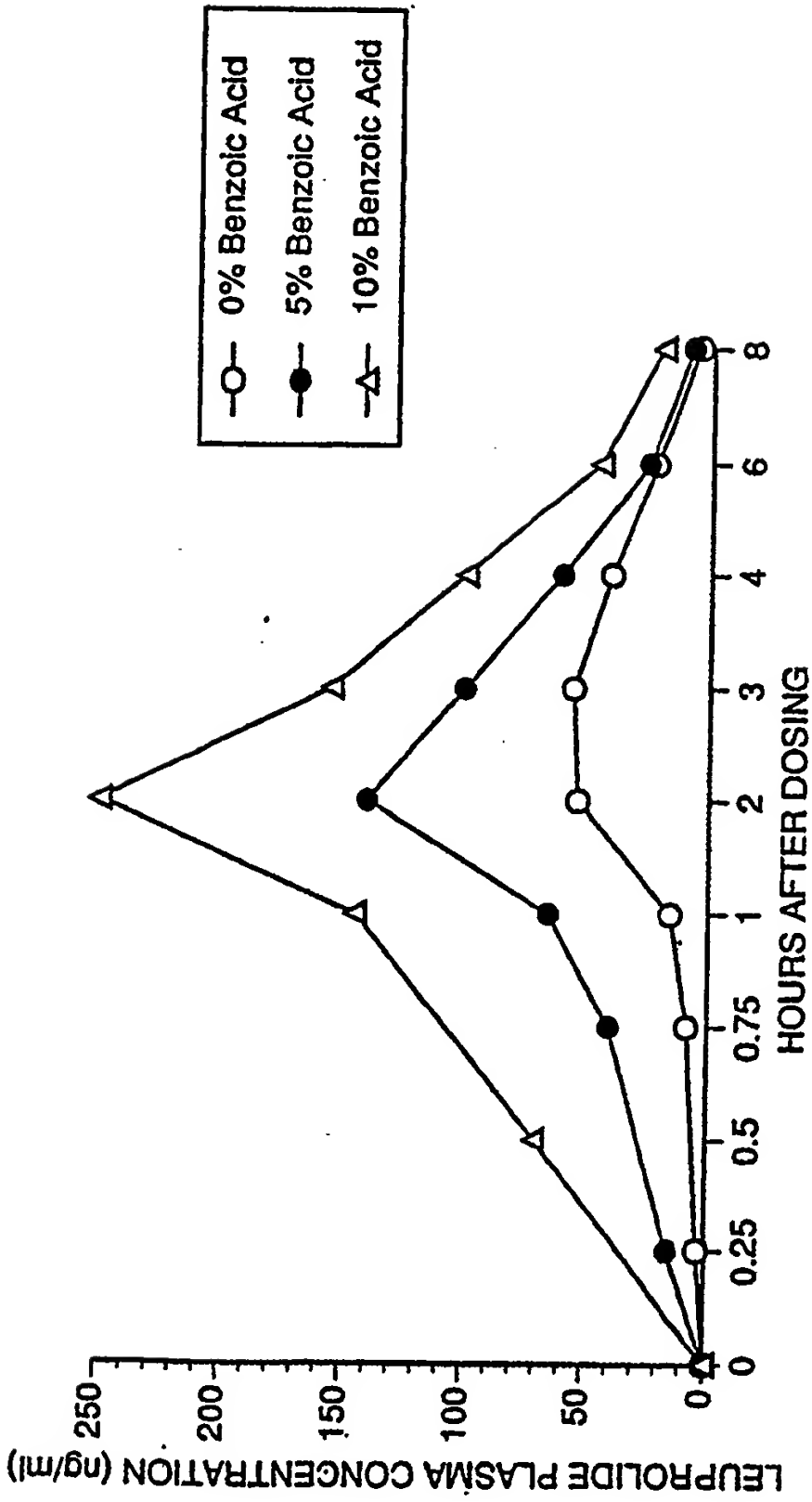


FIGURE 3

4/4

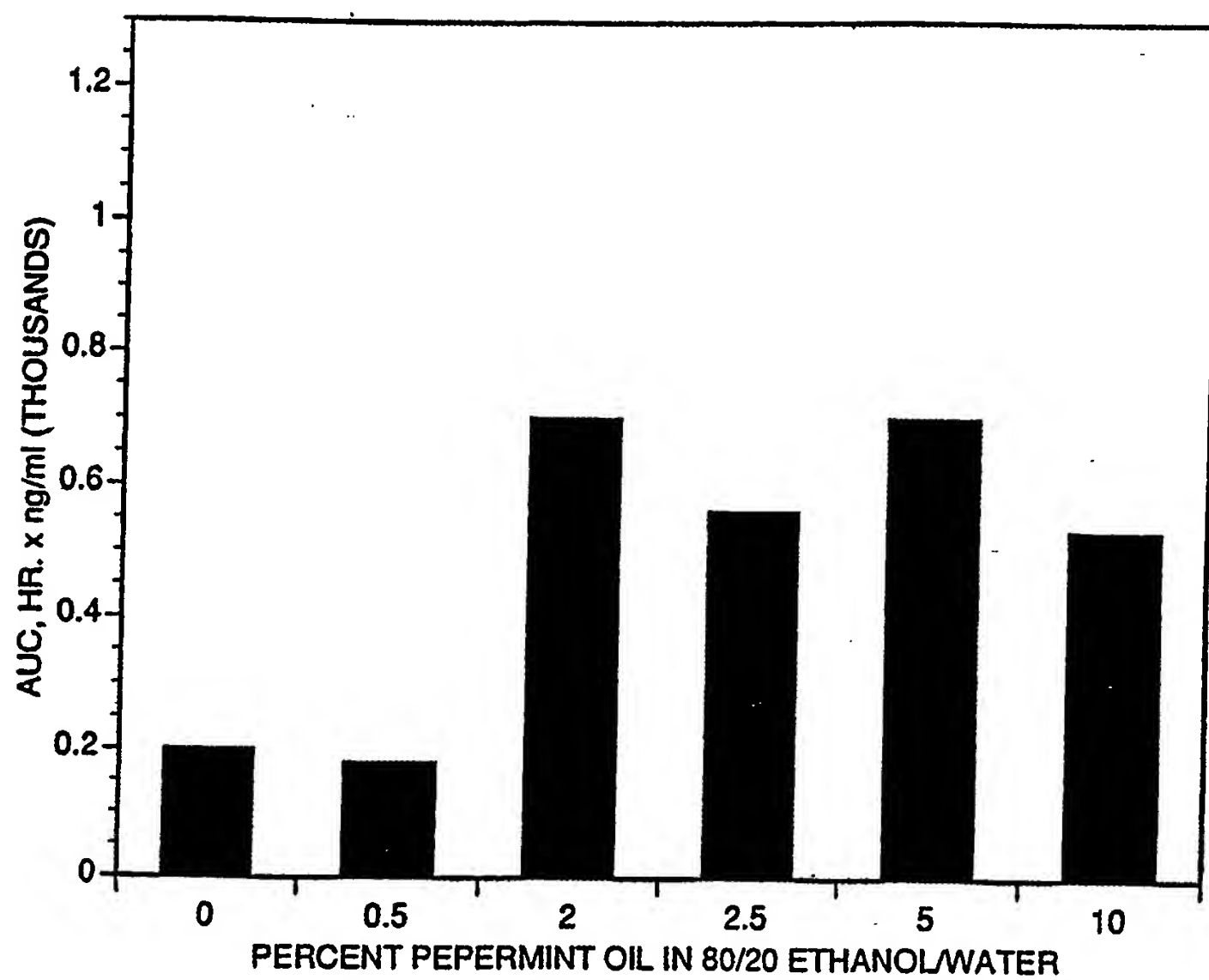


FIGURE 4

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/06944

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 37/02, 37/54; A01N 37/18; C12N 11/02, 15/16

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/94.62, 427, 428, 429, 435; 514/2, 15, 800, 803, 912; 435/180, 182, 201; 530/313; 623/4, 5; 930/10, 21, 130, DIG.695

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,244,946 (Rivier et al) 13 January 1981, col. 5, line 48.	1-10
Y	US, A, 4,382,922 (Rivier et al) 10 May 1983, see abstract	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be part of particular relevance	X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	&*	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

22 SEPTEMBER 1992

Date of mailing of the international search report

09 DEC 1992

Name and mailing address of the ISA/  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. NOT APPLICABLE

Authorized officer

CARLOS AZPURU

Telephone No. (703) 308-2351

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/06944

## A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

424/94.62, 427, 428, 429, 435; 514/2, 15, 800, 803, 912; 435/180, 182, 201; 530/313; 623/4, 5; 930/10, 21, 130, .  
DIG.695

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**